

Latent Class Analysis of Lifetime Depressive Symptoms in the National Comorbidity Survey

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Objective: Although clinical trials have documented the importance of identifying individuals with major depression with atypical features, there are fewer epidemiological data. In a prior report, the authors used latent class analysis (LCA) to identify a distinctive atypical depressive subtype; they sought to replicate that finding in the current study. **Method:** Using the National Comorbidity Survey data, the authors applied LCA to 14 DSM-III-R major depressive symptoms in the participants' lifetime worst episodes (N=2,836). Validators of class membership included depressive disorder characteristics, syndrome consequences, demography, comorbidity, personality/attitudes, and parental psychiatric history. **Results:** The best-fitting LCA solution had six classes. Four were combinations of atypicality and severity: severe atypical, mild atypical, severe typical, and mild typical. Syndrome severity (severe atypical and typical versus mild atypical and typical classes) was associated with a pronounced pattern of more and longer episodes, worse syndrome consequences, increased psychiatric comorbidity, more deviant personality and attitudes, and parental alcohol/drug use disorder. Syndrome atypicality (severe and mild atypical versus severe and mild typical classes) was associated with decreased syndrome consequences, comorbid conduct disorder and social phobia, higher interpersonal dependency and lower self-esteem, and parental alcohol/drug use disorder. **Conclusions:** As in prior reports, the atypical subtype of depression can be identified in epidemiological samples and, like typical depression, exists in mild and severe variants. Atypical depressive subtypes were characterized by several distinctive features. However, the correspondence between epidemiologically derived typologies of atypical depression and DSM-IV major depression with atypical features is not yet known.

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There have been numerous proposals for the subtyping of unipolar depression (1). Most typologies contained a common element, a subtype of unipolar

depression with marked typical, or vegetative, symptoms (e.g., poor appetite, loss of weight, insomnia, and anhedonia). Although there is general agreement about the existence of a typical subtype, there has been substantial disagreement on the classification of the remaining depressive subtypes (2).

Atypical depression has emerged as an important subtype of unipolar depression. In DSM-IV, atypical depression refers to major depression with preserved mood reactivity in response to positive events along with appetite increase, weight gain, hypersomnia, "leaden paralysis," and/or pathological rejection sensitivity. However, the term atypical depression is problematic because it has been used to describe a broad range of clinical presentations (3–7). The DSM-IV term has its origins in the work of a group of British psychiatrists (8, 9) who observed a subset of patients with "somewhat atypical depressive states" (8) characterized by a "reversed functional shift" (5) who re-

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TABLE 1. Class Membership (Total=2,836) and Endorsement Frequencies of the Variables in the Best-Fitting Latent Class Analysis (LCA) Solution Based on Data From the National Comorbidity Survey (NCS)^a

Variable	Class 1: Severe Typical (N=332)	Class 2: Mild Typical (N=488)	Class 3: Severe Atypical (N=169)	Class 4: Mild Atypical (N=305)	Class 5: Intermediate (N=881)	Class 6: Minimal Symptoms (N=661)
Prevalence in the NCS (%)	4	6	2	4	11	8
Variables used in LCA (%)						
DSM-III-R A criteria for major depression						
Feelings of depression	98	85	95	80	82	90
Loss of interest	91	51	85	51	68	11
Appetite decrease	88	73	39	2	11	4
Appetite increase	11	4	83	74	0	2
Weight decrease	77	82	40	1	6	4
Weight increase	0	2	84	68	0	0
Insomnia	92	75	87	57	55	27
Hypersomnia	31	8	54	23	26	3
Psychomotor agitation	35	20	49	10	9	5
Psychomotor retardation	62	6	56	11	14	0
Tiredness/lack of energy	92	34	92	58	59	11
Feelings of guilt or worthlessness	84	29	83	34	39	16
Trouble concentrating	94	42	85	41	53	7
Thoughts of death/suicide	77	39	78	39	56	25
Female gender	71	74	65	68	50	50
DSM-III-R major depression (%)	98	63	100	63	52	1
Number of depressive symptoms (range: 1–14)						
Mean	9.3	5.5	10.1	5.5	4.8	2.0
SD	1.3	1.4	1.5	1.6	1.5	0.9

^a Fifteen variables were entered into the LCA: 14 depressive symptoms that represented the nine “disaggregated” DSM-III-R A criteria for the lifetime worst episode plus gender. The best-fitting solution contained six classes.

sponded preferentially to monoamine oxidase inhibitors (MAOIs).

The subset of depressed patients with atypical symptoms has been investigated extensively in a series of randomized clinical trials at Columbia University (6, 7). Individuals meeting the Columbia criteria for atypical depression—included in DSM-IV with minor modifications—appear to respond preferentially to MAOIs in both acute (10, 11) and maintenance (12) treatment.

The construct of atypical depression is derived principally from clinical studies, although a few epidemiological studies are relevant. The lifetime prevalence of partial definitions of atypical depression (hyperphagia and hypersomnia) was 0.7% in the National Institute of Mental Health (NIMH)-Epidemiologic Catchment Area (ECA) dataset (13); in the Ontario Health Supplement dataset (14), the lifetime prevalence was 1.4% (0.9% with only atypical episodes and 0.5% with both typical and atypical episodes; atypicality was defined as hyperphagia, weight gain, and hypersomnia). Latent class analyses derived classes resembling atypical depression in the NIMH-ECA data (15) and in a community-based sample of female twins (past year prevalence=3.9%) (16).

Given the relative dearth of epidemiological data on atypical depression in contrast to the clinical data, we framed the following question: using data from a large probabalistic national sample and an approach similar to that employed by Kendler et al. (16), can the existence of an atypical depressive subtype be replicated?

METHOD

Sample

The National Comorbidity Survey (NCS) was a probabalistic survey of the U.S. population with a response rate of 82.4% (17). The NCS had two phases: a part 1 diagnostic interview (N=8,098) and a part 2 risk factor interview administered to a subsample (N=5,877) because of budgetary constraints. The part 2 interview was administered to all part 1 subjects aged 15–24 years, to all other subjects in part 1 with a lifetime diagnosis, and to a random subsample of the remaining subjects in part 1. The sampling and weighting procedures are described in detail elsewhere (17, 18). After complete description of the study, written informed consent was obtained.

Depressive Syndrome Assessment

In the NCS, depressive symptoms from the participants' worst lifetime episodes were assessed in the part 1 interview with the Composite International Diagnostic Interview (19, 20). Because of our interest in replication of our findings in the Virginia Twin Registry study, we took an approach as similar as possible to the approach in our previous report (16). To be included in the latent class analysis (LCA) in our present study, the worst lifetime episodes from the NCS (N=2,836) must have lasted at least 2 weeks, been associated with help-seeking or impairment, and contained one or more contemporaneous depressive symptoms. These depressive syndromes may or may not have met DSM-III-R criteria for major depression. To delineate typical and atypical symptoms, we “disaggregated” the nine DSM-III-R “A” criteria for major depression into 14 individual symptoms (table 1).

Latent Class Analysis

We used latent class analysis (LCA) (21–23) to determine empirically the typologies of depressive symptoms in the NCS. LCA is a “categorical analogue” to factor analysis and is particularly appropriate for data on the presence or absence of symptoms. Using a pro-

gram by Eaves et al. (22), we applied LCA to a 2,836×15 data matrix in an iterative manner. The rows corresponded to the 2,836 NCS participants with one depressive symptom or two or more co-occurring depressive symptoms. The 15 columns corresponded to responses of each subject to the 14 disaggregated major depression criteria and the subject's gender. We included gender to allow for the possibility of gender-related differences in symptoms. We first fit a one-class solution followed by a two-class solution, and so on, until we reached the "best" solution. We determined the best solution with reference to two criteria. First, the solution had to fit the data significantly better than had the previous class. The difference between the log-likelihood of the previous and the current class approximates a chi-square distribution; if this difference was greater than the critical chi-square statistic ($\chi^2=26.3$ for $\alpha=0.05$, $df=16$), then the current class provided a better fit to the data than had the previous class. Second, the Numerical Algorithms Group subroutine (E04UCF) (24) used by the LCA program for maximum likelihood minimization had to reach a valid solution (i.e., the E04UCF IFAIL parameter had to return as zero). We had relatively clear evidence in favor of a six-class solution as it was significantly better than all lower-order solutions and no seven-class solution was superior. Individual subjects were then assigned class membership based on the likelihood of their particular response profile.

LCA Validators

The next step was to determine whether there were important differences across the LCA classes. We used six sets of external validators not entered into the LCA: characteristics of the depressive disorder, symptom consequences, demography, comorbid psychiatric disorders, personality and attitudinal self-report data, and parental psychiatric history.

The first four sets of validators were assessed in the part 1 interview. The Comprehensive International Diagnostic Interview/DSM-III-R diagnoses available were major depression, bipolar disorder, conduct disorder, antisocial personality, panic disorder, agoraphobia without panic disorder, generalized anxiety disorder, social phobia, simple phobia, alcohol dependence, and non-alcohol/non-nicotine drug dependence (17). The part 2 interview ($N=5,877$) yielded the diagnosis of posttraumatic stress disorder (PTSD) (18) and empirically abbreviated forms of several personality and attitudinal measures: neuroticism, extraversion, and openness to experience (25); internal and external locus of control (26); self-esteem and self-reliance (27); fatalism (28); and interpersonal dependency and interpersonal conformity (29). All scores were standardized before analysis.

We evaluated a history of depressive disorder, alcoholism, and drug use disorder for the biological parents of the respondent in the part 2 interview by using standardized criteria (30, 31).

Statistical Analyses

The goal of these analyses was to attempt to validate LCA class membership. We were particularly interested in whether the classes found in the Virginia Twin Registry (VTR) sample (16) could be replicated. We first compared the six LCA classes in terms of depressive symptoms, characteristics, and symptom consequences. We then focused on demography, psychiatric comorbidity, personality and attitudes, and parental psychiatric history in reference to a comparison group of the 5,262 NCS subjects not entered into the LCA because they denied lifetime depressive symptoms. We used logistic regression and multiple regression models (32) including the NCS weighting variables and controlling for the effects of age, race, and gender.

Multiple Comparisons

These analytic aims necessitated a large number of statistical comparisons and, given the large number of validators, the overall type I error was inflated. We employed a two-tailed significance level of 0.01 to compensate partially for the number of comparisons. More importantly, as the major aim was to validate the empirically derived LCA classes, the pattern of differences among the validators (rather than an isolated difference) had to support its existence as a valid entity.

RESULTS

Class Descriptions

Table 1 depicts the observed class membership and endorsement frequencies of the 14 disaggregated DSM-III-R depressive symptoms in the best-fitting LCA solution. These data are from the 2,836 participants (35.0%) in the NCS with one or more contemporaneous depressive symptoms in the lifetime worst episode. Class 1 (4% of total NCS participants) was characterized by a very high lifetime occurrence of major depression (98%) and high endorsement rates for most of the 14 disaggregated symptoms of major depression. We termed class 1 "severe typical" because of the nearly universal presence of major depression and the preponderance of classical depressive symptoms (i.e., weight and appetite loss, insomnia, psychomotor retardation, anergia, and poor concentration). Class 2 (6% of total NCS participants) was also characterized by classical depressive symptoms, although fewer subjects (63%) met criteria for major depression. We thus termed class 2 "mild typical." Like class 1, class 3 (2% of total NCS participants) was characterized by many depressive symptoms, and 100% of this class met criteria for major depression; however, the symptom pattern was more characterized by appetite increase and weight gain. Both insomnia and hypersomnia were prevalent. We termed class 3 "severe atypical." Like class 3, class 4 (4% of total NCS participants) was characterized by atypical depressive symptoms with 63% meeting criteria for major depression. We termed class 4 "mild atypical." Class 5 (labeled "intermediate") was the most prevalent (11% of total NCS participants) and was characterized by intermediate occurrence of major depression (52%) with prominent symptoms of low mood, loss of interest, insomnia, loss of energy, and thoughts of death. Class 6 (8% of total NCS participants) had low endorsement rates for all depressive symptoms except the stem question (whether the subject felt depressed) and a very low occurrence of major depression (1%, labeled "minimal symptoms"). The first four classes were predominantly female, whereas the gender ratios for the last two classes were equal.

Validator Overview

Table 2 depicts the syndrome characteristics for the six empirically derived LCA classes. Age at onset was similar across groups, although the severe typical and severe atypical classes tended to be associated with recurrent and persistent episodes of mood disturbance accompanied by considerable behavioral and syndrome consequences.

Table 3 presents descriptive data for demography, comorbidity, personality/attitudes, and parental psychiatric history of members of the six LCA classes in comparison with NCS subjects who denied depressive

TABLE 2. Data on Syndrome Characteristics and Consequences for the Six Classes Empirically Derived From Latent Class Analysis (LCA) of Data From the National Comorbidity Survey (NCS)

Syndrome Characteristic or Consequence	Class 1: Severe Typical (N=332)		Class 2: Mild Typical (N=488)		Class 3: Severe Atypical (N=169)		Class 4: Mild Atypical (N=305)		Class 5: Intermediate (N=881)		Class 6: Minimal Symptoms (N=661)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Characteristics												
Age at onset (years)	23.1	9.8	23.9	9.0	22.5	10.0	23.4	9.5	23.1	9.4	23.8	9.6
Number of episodes	9.3	19.4	4.5	9.8	12.4	23.3	5.3	9.7	6.8	15.9	6.0	14.6
Longest episode (months)	22.6	56.8	11.2	31.9	30.2	59.3	12.4	44.7	11.3	30.0	13.0	35.3
Number of consequences (range: 0–9)	3.6	2.5	2.1	2.0	3.5	2.5	1.5	1.9	1.8	1.9	2.0	2.1
Type of consequences												
	%		%		%		%		%		%	
Saw mental health worker	48		30		51		25		28		27	
Saw other professional	30		19		29		14		19		18	
Took medication	36		19		40		13		17		21	
Interference with life or activities	60		32		66		22		27		25	
Kept from working or socializing	70		44		69		35		41		41	
Hospitalization	19		7		20		3		7		9	

symptoms (N=5,262). There were highly significant differences across these seven groups for all of these variables except age at interview and fatalism.

The six empirically derived LCA classes can be considered as the four combinations of atypical/typical symptoms and severe/mild symptoms as well as the intermediate and minimal symptoms classes.

Validation: Atypicality and Severity

In the following analysis, we focused on four LCA classes (severe atypical, mild atypical, severe typical, and mild typical) to understand more clearly the influence of atypicality and severity. We created three variables that were used in the subsequent analyses. “Atypicality” coded the presence/absence of atypical symptoms (1=severe and mild atypical classes, 0=otherwise), “severity” coded the presence/absence of severe symptoms (1=severe atypical and typical classes, 0=otherwise), and the interaction term was the product of the atypicality and severity variables (1=severe atypical, 0=otherwise).

Table 4 summarizes these analyses. The main effect of severity had considerable impact across the majority of the validators. The severe atypical and severe typical classes were associated with more and longer episodes; more syndrome consequences; substantial comorbidity; increased conformity, dependency, neuroticism, and external locus of control; lower self-esteem; and increased parental alcohol/drug use disorders.

The main effect of atypicality was more complex. First, there were fewer significant differences for atypicality than for severity, suggesting that the latter was a more potent discriminator. Second, independent of severity, the atypical classes were characterized by decreased syndrome consequences, increased risk for conduct disorder and social phobia but decreased risk for PTSD, personality traits of higher interpersonal dependency and lower self-esteem, and a parental history of alcohol/drug use disorder. Finally, the interaction of atypicality and severity was associated with increased

interference and total symptom consequences, decreased social phobia, and increased PTSD.

Validation: Intermediate and Minimal Symptoms Classes

The intermediate and minimal symptom classes were the most prevalent of the LCA classes, although their symptom endorsement patterns were quite different (table 1). Statistical comparisons of these two classes for the external validators in tables 2 and 3 revealed essentially no differences between them (data not shown). However, both of these classes had a surprisingly high degree of syndrome consequences (table 2) which were equivalent to or, occasionally, exceeded those of the mild typical and mild atypical classes. In regard to comorbidity (table 3), conduct disorder, antisocial personality, alcohol dependence, and drug dependence were particularly prevalent in the intermediate and minimal symptom classes.

DISCUSSION

Subtypes of Depression

Application of LCA to the lifetime depressive symptom data from the NCS yielded six interpretable classes. Four of these classes were defined by the combinations of severity (severe versus mild symptoms) and atypicality (atypical versus typical symptoms); the remaining 2 classes were distinctive. Identification of depressive subtypes defined by mild and severe symptoms is neither profound nor surprising and has been widely documented in prior clinical and epidemiological studies by use of a host of methodological approaches.

Atypical Depression

The particularly interesting result from this study was the identification of depressive classes defined

TABLE 3. Demographic Characteristics, Comorbidity, Personality and Attitudes, and Parental Psychiatric History for the Six Classes of Atypical Depression Derived From Latent Class Analysis (LCA) of Data From the National Comorbidity Survey (NCS)^a

Feature	Class 1: Severe Typical (N=332)	Class 2: Mild Typical (N=488)	Class 3: Severe Atypical (N=305)	Class 4: Mild Atypical (N=305)	Class 5: Intermediate (N=881)	Class 6: Minimal Symptoms (N=661)	Subjects With No Symptoms (N=5,262)	Analysis			
								F	χ^2	df	p
Demography											
Age (years)								1.71		6, 8091	0.11
Mean	34.3	33.0	34.0	34.7	33.0	33.3	33.2				
SD	9.9	9.4	10.7	10.9	10.2	11.3	11.0				
Ethnic group (%)									74.7	18	<0.0001
Caucasian	84	73	79	81	76	83	74				
African American	6	10	7	10	10	7	13				
Hispanic	9	12	10	8	10	7	10				
Other	1	5	4	1	5	3	4				
Comorbid disorders (%)											
Bipolar I disorder	12	4	12	3	4	2	0.10		432.5	6	<0.0001
Conduct disorder	18	10	19	19	22	22	10		172.1	6	<0.0001
Antisocial personality	6	2	8	1	6	10	2		173.6	6	<0.0001
Panic disorder	17	7	16	6	8	4	1		431.3	6	<0.0001
Agoraphobia without panic disorder	15	11	15	8	8	9	3		403.6	6	<0.0001
Generalized anxiety disorder	29	10	35	7	10	8	1		936.8	6	<0.0001
Social phobia	31	19	32	31	24	20	8		465.7	6	<0.0001
Simple phobia	30	22	36	25	18	14	6		499.8	6	<0.0001
Posttraumatic stress disorder ^b	22	17	34	9	13	11	3		379.2	6	<0.0001
Alcohol dependence	28	16	32	21	23	23	10		296.3	6	<0.0001
Drug dependence	16	7	20	7	15	16	4		279.3	6	<0.0001
Number of disorders ^c (range: 1–10)											
Mean	2.0	1.0	2.3	1.4	1.4	1.3	0.5	257.7		6, 8091	<0.0001
SD	1.4	1.1	1.7	1.2	1.3	1.5	0.9				
Personality or attitude variable (z score) ^b											
Conformity	0.31	0.03	0.36	0.20	0.16	0.09	-0.14	23.6		6, 5870	<0.0001
Dependency	0.41	0.11	0.42	0.31	0.22	0.13	-0.18	41.9		6, 5870	<0.0001
Extraversion	-0.14	-0.02	-0.21	-0.15	-0.22	-0.07	0.07	11.2		6, 5870	<0.0001
Neuroticism	0.76	0.37	0.76	0.45	0.40	0.34	-0.28	143.4		6, 5870	<0.0001
External locus of control	0.16	0.00	0.15	0.06	0.06	0.09	-0.11	8.43		6, 5870	<0.0001
Internal locus of con- trol	-0.13	-0.05	-0.02	-0.25	-0.25	-0.07	0.09	14.1		6, 5870	<0.0001
Fatalism	0.04	0.06	0.09	0.00	-0.01	-0.01	-0.03	0.81		6, 5870	0.57
Openness	0.15	0.13	0.06	0.01	0.05	0.07	-0.05	4.15		6, 5870	0.0004
Self-esteem	-0.77	-0.22	-0.87	-0.54	-0.43	-0.27	0.28	151.7		6, 5870	<0.0001
Self-reliance	-0.21	-0.05	-0.19	-0.13	-0.23	-0.18	0.07	14.4		6, 5870	<0.0001
Parental psychiatric history (%)											
Major depression ^b									398.5	12	<0.0001
No parent	46	53	45	53	53	61	77				
One parent	40	34	39	36	37	30	20				
Both parents	13	13	16	11	10	10	4				
Alcohol/drug disorder ^b									160.7	12	<0.0001
No parent	65	73	59	63	70	74	82				
One parent	30	23	32	35	29	23	17				
Both parents	5	4	9	2	4	3	2				

^a The data shown reflect weighting variables. The statistics and p values are results of ANOVAs (age and personality/attitude variables) or chi-square tests across the seven groups.

^b Assessed in the part 2 interview.

^c Does not include major depression or posttraumatic stress disorder.

principally by the atypicality of the symptoms reported. Depressive symptoms with an atypical character or a “reversed functional shift” (5) (i.e., appetite increase, weight gain, hypersomnia, and psychomotor agitation) constituted one side of the atypicality dichotomy. The symptoms that contributed to the other

side of this dichotomy were typical, or vegetative, in nature (i.e., appetite decrease, weight loss, insomnia, and psychomotor retardation) resembling a “functional shift” (33).

Our principal interest in conducting this study was whether our prior finding in the VTR (16) could be re-

TABLE 4. Analysis of the Influence of Atypicality and Severity of Depressive Symptoms on Validators of Latent Class Analysis (LCA) of Data From the National Comorbidity Survey (N=2,836)^a

Validator	Regression Coefficients ^b								
	Atypicality			Severity			Interaction		
	Coefficient	SE	Direction of Effect	Coefficient	SE	Direction of Effect	Coefficient	SE	Direction of Effect
Syndrome characteristics									
Age at onset (years)	1.80	0.76		1.08	0.73		-3.41	1.20	
Number of episodes	0.42	1.07		2.53*	1.07	(↑)	2.60	1.74	
Longest episode	0.35	2.88		1.80***	2.86	(↑)	-1.08	4.65	
Syndrome consequences									
Saw mental health worker	-0.28	0.17		0.76***	0.15	(↑)	0.40	0.25	
Saw other professional	-0.22	0.21		0.66***	0.18	(↑)	0.03	0.30	
Took medication	-0.46	0.22		0.89***	0.17	(↑)	0.66	0.29	
Interference with life or activities	-0.36	0.18		1.25***	0.15	(↑)	1.03***	0.26	(↑)
Kept from working or socializing	-0.54**	0.15	(↓)	1.09***	0.15	(↑)	0.52	0.25	
Hospitalization	-0.95	0.38		1.00***	0.23	(↑)	0.97	0.45	
Number of consequences	-0.54**	0.15	(↓)	1.41***	0.15	(↑)	0.70**	0.25	(↑)
Demography									
Female gender	-0.07	0.09		-0.29	0.12		0.57	0.26	
Ethnicity ^c									
Caucasian									
African American	-0.02	0.21		-0.44	0.22		0.04	0.45	
Hispanic	-0.27	0.20		-0.08	0.19		0.57	0.40	
Other	-0.20	0.35		-0.59	0.38		2.52	1.04	
Comorbidity									
Bipolar I disorder	-0.17	0.24		1.25***	0.24	(↑)	0.71	0.52	
Conduct disorder	0.44**	0.16	(↑)	0.33	0.16		-0.45	0.33	
Antisocial personality	0.25	0.31		1.62***	0.35	(↑)	0.81	0.72	
Panic disorder	-0.13	0.19		1.03***	0.19	(↑)	0.16	0.39	
Agoraphobia without panic disorder	-0.20	0.19		0.60**	0.18	(↑)	0.22	0.37	
Generalized anxiety disorder	0.01	0.16		1.55***	0.16	(↑)	0.69	0.34	
Social phobia	0.74***	0.17	(↑)	0.75***	0.17	(↑)	-0.73**	0.27	(↓)
Simple phobia	0.26	0.13		0.50***	0.13	(↑)	-0.03	0.27	
Posttraumatic stress disorder	-0.73*	0.25	(↓)	0.40	0.19		1.28***	0.33	(↑)
Alcohol dependence	0.27	0.14		0.60***	0.14	(↑)	0.04	0.28	
Drug dependence	0.13	0.18		0.95***	0.18	(↑)	0.30	0.37	
Personality and attitudes									
Conformity	0.13	0.06		0.24***	0.06	(↑)	-0.15	0.12	
Dependency	0.14*	0.05	(↑)	0.23***	0.05	(↑)	-0.21	0.11	
Extraversion	-0.10	0.06		-0.08	0.06		0.03	0.12	
Neuroticism	0.06	0.06		0.36***	0.06	(↑)	-0.11	0.12	
External locus of control	0.04	0.06		0.15*	0.06	(↑)	-0.14	0.12	
Internal locus of control	-0.07	0.06		0.03	0.06		0.29	0.12	
Openness	-0.10	0.06		0.03	0.05		0.12	0.11	
Self-esteem	-0.24***	0.06	(↓)	-0.48***	0.06	(↓)	0.26	0.13	
Self-reliance	-0.05	0.06		-0.11	0.06		0.08	0.12	
Parental psychiatric history									
Major depression	-0.02	0.15		0.18	0.14		0.15	0.23	
Alcohol/drug use disorder	0.40*	0.12	(↑)	0.36*	0.12	(↑)	-0.13	0.25	

^a As described in the text, these analyses were limited to four classes (severe atypical, mild atypical, severe typical, and mild typical). Group sizes are given in tables 1, 2, and 3.

^b The atypicality variable coded the presence or absence of atypical symptoms (1=severe and mild atypical classes, 0=otherwise). The severity variable coded the presence or absence of severe symptoms (1=severe typical and atypical classes, 0=otherwise). The interaction term was the product of the atypicality and severity variables (1=severe atypical, 0=otherwise). The values shown are the coefficients and standard errors from logistic regression (nominal and ordinal validators) or multiple regression analyses (continuous variables). If the interaction term was not significant, it was omitted. To aid in interpretation, the arrows indicate the signs of the regression coefficients (↑=positive, ↓=negative). All analyses used the "normalized" NCS design weights and, except for the demographic variables, were controlled for the effects of age, gender, and race.

^c For ethnicity, Caucasian subjects formed the reference group.

*p=0.01.

**p=0.001.

***p=0.0001.

produced in a different sample by a similar analytic approach (i.e., the use of LCA and similar item definitions). The NCS and the VTR are similar in that both are population based and used structured diagnostic instruments. However, these similarities are overshadowed by many differences:

1. The NCS was a probability sample of the continental U.S., whereas the VTR consisted solely of twins born in Virginia.

2. The NCS consisted of male and female subjects of any ethnicity aged 15–54 years, whereas the VTR report was on Caucasian women aged 22–59 years.

TABLE 5. Comparison of Classes of Atypical Depression Derived From Latent Class Analysis (LCA) in the National Comorbidity Survey (NCS) and Virginia Twin Registry (VTR) (16)

Variable	NCS ^a				VTR ^b		
	Class 1: Severe Typical	Class 2: Mild Typical	Class 3: Severe Atypical	Class 4: Mild Atypical	Severe Typical	Mild Typical	Atypical
	Typical	Typical	Atypical	Atypical	Typical	Typical	Atypical
Vegetative symptoms	Typical	Typical	Atypical	Atypical	Typical	Typical	Atypical
Mean number of symptoms (range: 1–14)	9.3	5.5	10.1	5.5	9.9	6.3	6.2
Major depression (%)	98	63	100	63	97	66	46
Marked role interference (%)	60	32	66	22	44	22	16
Female gender (%)	71	74	65	68	100	100	100
Comorbid generalized anxiety disorder and panic	Much higher	Higher	Much higher	Higher	Very much higher	Much higher	Higher
Other lifetime disorders	Much higher	Higher	Much higher	Higher	Higher ^c	—	Higher ^d
Extraversion	Lower	Lower	Lower	Lower	Normal	Normal	Lower
Neuroticism	Much higher	Higher	Much higher	Higher	Higher	Higher	Higher

^a Classes based on 14 disaggregated DSM-III-R major depression symptoms in the worst lifetime episode.

^b Classes based on 14 disaggregated DSM-III-R major depression symptoms in the year before interview.

^c Phobia.

^d Bulimia.

3. The NCS depressive symptoms were for the lifetime worst episode of at least 2 weeks' duration, whereas the VTR data were for a period in the prior year that had lasted at least 5 days.

4. Depressive symptoms were coded for all VTR subjects but only for a subset of the NCS participants.

5. Although the NCS interview (based on the Composite International Diagnostic Interview) and VTR interview (based on the Structured Clinical Interview for DSM-III-R [34]) both assessed the DSM-III-R criteria for major depression, the two interviews were considerably different in structure, item wording, and format.

Thus, given that the dissimilarities were greater than the similarities between the VTR and the NCS, it is notable that we were able to reproduce the existence of the atypical classes, one of the key findings from our prior report (34).

In the depression treatment literature, the clinical importance of identifying a subset of depressed patients with atypical symptoms is supported by expert opinion (8, 9) and clinical trials (10–12, 35), although not in all studies (5). Patients with atypical depression may constitute a distinct neurobiological subset (36). However, given the many different uses of the term atypical over time (6, 7), a critical question is the degree to which the atypical subtype of depressive symptoms identified in this study and in our prior report (16) overlaps with the Columbia/DSM-IV definitions.

We possess insufficient information to answer this question as we lacked data on all elements of the Columbia/DSM-IV criteria for atypical depression (i.e., mood reactivity, leaden paralysis, and enduring rejection sensitivity). The atypical subtypes we identified were characterized by appetite increase, weight gain, hypersomnia, and, to some extent, psychomotor retardation, which overlap with the Columbia/DSM-IV criteria. Of note, the focus on mood reactivity in the Columbia/DSM-IV criteria is not found in other defini-

tions of atypicality that highlight instead symptoms of a reversed functional shift (4, 5, 8, 9).

If the overlap between the clinically and epidemiologically defined atypical depressive symptoms is reasonable, these convergent findings—epidemiological dissection of atypical classes in several distinct studies—combined with the clinical utility of atypical depressive symptoms, constitute a compelling rationale for the existence of an atypical subtype and its inclusion in any typology of unipolar depression.

Comparing the NCS and VTR Results

To facilitate comparison, table 5 summarizes the results of this NCS-based investigation and the VTR report (16). The VTR report described severe and mild typical LCA classes that were fairly similar to their NCS counterparts in symptoms, mean number of symptoms, the proportion with major depression, and the proportion reporting role interference. The VTR atypical class was most similar to the NCS mild atypical class. The NCS severe atypical class had no counterpart in the VTR, perhaps because the NCS was larger or used a longer time frame.

Kendler et al. (16) noted several differences between the VTR atypical class and the other classes—i.e., the atypical class was less likely to have comorbid general affective disorder and panic disorder and had decreased extraversion. With the identification in the NCS of a severe atypical class as well as a mild atypical class (similar to the VTR atypical class), the differences in the VTR appear to be more related to severity than to atypicality. The NCS results also differ from those of the VTR in that neuroticism was elevated in the NCS classes, particularly in the severe classes. The VTR report also noted that the atypical class had increased body mass index, risk of bulimia, moderate risk of future major depression, moderate symptom stability over time, and high monozygotic twin concordance. These data were not available in the NCS.

Typical Versus Atypical Depression

Perhaps the most informative comparisons are those between atypicality and severity (tables 3 and 4). Most differences across the four classes defined by atypicality and severity were related to severity. The main effect of severity (table 4) was associated with worse episodes, more syndrome consequences, increased comorbidity, more deviant personality traits, and a parental history of alcohol/drug use disorders. These differences were in the anticipated direction and validated the severe versus mild LCA class distinction.

The main effect of atypicality was less frequently significant, although the atypical classes were characterized by decreased syndrome consequences, comorbid conduct disorder and social phobia (but decreased PTSD), higher interpersonal dependency and lower self-esteem, and a parental history of alcohol/drug use disorder. These results suggest that atypicality—although unexpectedly similar to typicality—may have several distinct characteristics. The association of atypicality with parental alcohol/drug use disorders is reminiscent of Winokur's depression spectrum disease (37).

We expected to find that the atypical classes were characterized by a distinct personality profile—perhaps akin to neurotic depression (3). Although atypicality had little impact on many personality/attitudinal attributes, the atypical classes had greater interpersonal dependency and lower self-esteem suggesting that there may be a specific personality typology associated with atypical depression.

From some prior studies of atypical depression (2, 4, 36), we expected to find an overrepresentation of women in the severe and mild atypical classes. As in other reports (13, 14), we identified no significant gender differences.

Intermediate and Minimal Symptom Classes

The occurrence of these "subthreshold" classes (together comprising 19% of the subjects in the NCS) and the rather high proportion of each class that reported recurrent and enduring symptoms along with help-seeking behavior or marked symptom consequences were surprising. We know little about the so-called minor depressive disorders. The characteristics of these classes—particularly the equal gender ratio—would argue for further specific study.

We put forward three speculations about these classes. First, studies from the NCS (38) and the VTR (39) suggest that depressive states that do not quite meet the DSM-III-R criteria differ from more definitive major depression quantitatively and not qualitatively. These classes might represent *formes frustes* of major depression. In addition, subsyndromal depressive symptoms are associated with considerable social morbidity (40, 41) and an increased risk for first-onset major depression (42). Second, as the diagnosis of major depression in epidemiological samples has modest reli-

ability (43, 44), these classes might contain individuals who in fact had major depression but who were coded as having subthreshold symptoms. Finally, these two classes were notable for their increased prevalence of alcohol and drug dependence; depressive symptoms could have represented substance-induced mood disorders.

Caveats

The depressive symptoms we studied were during the worst lifetime episode. We had no information about whether subsequent or prior episodes had a similar or different pattern of typical and atypical symptoms. Moreover, some of our findings may have been due to chance given the large number of statistical comparisons performed.

REFERENCES

1. Kendell RE: The classification of depressions: a review of contemporary confusion. *Br J Psychiatry* 1976; 129:15–28
2. Davidson J, Woodbury MA, Pelton S, Krishnan R: A study of depressive typologies using grade of membership analysis. *Psychol Med* 1988; 18:179–189
3. Akiskal HS, Bitar AH, Puzantian VR, Rosenthal TL, Walker PW: The nosological status of neurotic depression. *Arch Gen Psychiatry* 1978; 35:756–766
4. Davidson JRT, Miller RD, Turnbull CD, Sullivan JL: Atypical depression. *Arch Gen Psychiatry* 1982; 39:527–534
5. Paykel ES, Parker RR, Rowan PR, Rao BM, Taylor CN: Nosology of atypical depression. *Psychol Med* 1983; 13:131–139
6. Stewart JW, McGrath PJ, Rabkin JG, Quitkin FM: Atypical depression: a valid clinical entity? *Psychiatr Clin North Am* 1993; 16:479–495
7. Rabkin JG, Stewart JW, Quitkin FM, McGrath PJ, Harrison WM, Klein DF: Should atypical depression be included in DSM-IV? in *DSM-IV Sourcebook*. Edited by Widiger TA, Frances AJ, Pincus HA, Ross R, First MB, Davis WW. Washington, DC, American Psychiatric Association, 1994, pp 239–260
8. West ED, Dally PJ: Effects of iproniazid in depressive syndromes. *BMJ* 1959; 1:1491–1494
9. Sargent W: Some newer drugs in the treatment of depression and their relation to other somatic treatments. *Psychosomatics* 1960; 1:14–17
10. Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. *Am J Psychiatry* 1988; 145:306–311
11. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF: Atypical depression, panic attacks, and response to imipramine and phenelzine. *Arch Gen Psychiatry* 1990; 47:935–941
12. Stewart JW, Tricamo E, McGrath PJ, Quitkin FM: Prophylactic efficacy of phenelzine and imipramine in chronic atypical depression: likelihood of recurrence on discontinuation after 6 months' remission. *Am J Psychiatry* 1997; 154:31–36
13. Horwath E, Johnson J, Weissman MM, Hornig CD: The validity of major depression with atypical features based on a community study. *J Affect Disord* 1992; 26:117–126
14. Levitan RD, Lesage A, Parikh SV, Goering P, Kennedy SH: Reversed neurovegetative symptoms of depression: a community study of Ontario. *Am J Psychiatry* 1997; 154:934–940
15. Eaton WW, Dryman A, Sorenson A, McCutcheon A: DSM-III major depressive disorder in the community: a latent class analysis. *Br J Psychiatry* 1989; 155:48–54

16. Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC: The identification and validation of distinct depressive syndromes in a population-based sample of female twins. *Arch Gen Psychiatry* 1996; 53:391–399
17. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51:8–19
18. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB: Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1996; 52:1048–1060
19. World Health Organization: Composite International Diagnostic Interview (CIDI), version 1.0. Geneva, WHO, 1990
20. Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, Sartorius N, Towle LH: The Composite International Diagnostic Interview: an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatry* 1988; 45:1069–1077
21. McCutcheon AL: Latent Class Analysis. Beverly Hills, Calif, Sage Publications, 1987
22. Eaves LJ, Silberg JL, Hewitt JK, Rutter M, Meyer JM, Neale MC, Pickles A: Analyzing twin resemblance in multisymptom data: genetic applications of a latent class model for symptoms of conduct disorder in juvenile boys. *Behav Genet* 1993; 23:5–19
23. Yang I, Becker MP: Latent variable modeling of diagnostic accuracy. *Biometrics* 1997; 53:948–958
24. Numerical Algorithms Group: NAG FORTRAN Library Manual. Oxford, England, Numerical Algorithms Group, 1993
25. Goldberg LR: The development of markers for the big-five factor structure. *Psychol Assess* 1992; 4:26–42
26. Levenson H: Multidimensional locus of control in psychiatric patients. *J Consult Clin Psychol* 1973; 41:397–404
27. Rosenberg M: Society and the Adolescent Self-Image. Princeton, NJ, Princeton University Press, 1965
28. Schwartz S, Robinson MM: Attitudes toward poverty during undergraduate education. *J Social Work Education* 1991; 27: 290–296
29. Hirschfeld RM: A measure of interpersonal dependency. *J Pers Assess* 1977; 41:610–618
30. Endicott J, Andreasen NC, Spitzer RL: Family History Research Diagnostic Criteria, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1978
31. Kendler KS, Davis CG, Kessler RC: The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *Br J Psychiatry* 1997; 170:541–548
32. SAS/STAT User's Guide, version 6, 4th ed. Cary, NC, SAS Institute, 1989
33. Pollitt JD: Suggestions for a physiological classification of depression. *Br J Psychiatry* 1965; 111:489–495
34. Spitzer RL, Williams JBW, Gibbon M, First MB: The Structured Clinical Interview for DSM-III-R (SCID), I: history, rationale, and description. *Arch Gen Psychiatry* 1992; 49:624–629
35. Thase ME, Carpenter L, Kupfer DJ, Frank E: Atypical depression: diagnostic and pharmacologic controversies. *Psychopharmacol Bull* 1991; 27:17–22
36. Asnis GM, McGinn LK, Sanderson WC: Atypical depression: clinical aspects and noradrenergic function. *Am J Psychiatry* 1995; 152:31–36
37. Winokur G: Unipolar depression: is it divisible into autonomous subtypes? *Arch Gen Psychiatry* 1979; 36:47–52
38. Kessler RC, Zhao S, Blazer DG, Swartz M: Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord* 1997; 45: 19–30
39. Kendler KS, Gardner CO Jr: Boundaries of major depression: an evaluation of DSM-IV criteria. *Am J Psychiatry* 1998; 155: 172–177
40. Johnson J, Weissman MM, Klerman GL: Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* 1992; 267:1478–1483
41. Judd LL, Paulus MP, Wells KB, Rapaport MH: Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am J Psychiatry* 1996; 153:1411–1417
42. Horwath E, Johnson J, Klerman GL, Weissman MM: Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch Gen Psychiatry* 1992; 49:817–823
43. Bromet EJ, Dunn LO, Connell MM, Dew MA, Schulberg HC: Long-term reliability of diagnosing lifetime major depression in a community sample. *Arch Gen Psychiatry* 1986; 43:435–440
44. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ: The lifetime history of major depression in women: reliability of diagnosis and heritability. *Arch Gen Psychiatry* 1993; 50:863–870